REMARKS

Claims 1-10 were pending. All pending claims were rejected in the Office Action. Clams 1-10 are cancelled herein. New claims 11-16 have been added. No new matter has been added thereby. Specifically, support for new claim 11 can be found, *inter alia*, in claims 1, 2, 7, and 8 as originally filed, on page 5, line 30 to page 6, line 10, of the application as filed, and the examples of the application as filed, all of which show the use of a modified Fab' fragment as the basis for the exemplified antibody fragment. New claims 12-16 correspond to claims 3, 4, 5, 9, and 10, respectively, as originally filed.

Rejections Under 35 USC § 112, Second Paragraph

Claims 3-7 were rejected under 35 USC § 112, second paragraph, as allegedly indefinite. Applicants traverse these rejections to the extent they are applicable to the new claims.

Claims 3 and 4 were alleged to be indefinite in view of the recitation of the word "optionally." New claims 12 and 13 correspond to original claims 3 and 4. The Office alleged it is not clear what the exact meaning of the term "optional" is, and that it is confusing what is meant by "optionally substituted." The Office stated it is confusing whether the phrase is intended to modify the term straight or branched chains.

First, Applicants note that the term is "optionally substituted," not "optional." Second, it is clear that the term modifies both of the terms straight and branched. Nonetheless, to further clarify, Applicants have added a comma after "optionally substituted." Finally, the word "optionally" is not, *a prior*, indefinite. In *Ex parte Cordova*, 10 USPQ2d 1949 (Bd. Pat. App. & Inter. 1989) the language "containing A, B, and optionally C" was considered acceptable alternative language because there was no ambiguity as to which alternatives were covered by the claim. A similar holding was reached with regard to the term "optionally" in *Ex parte Wu*, 10 USPQ2d 2031 (Bd. Pat. App. & Inter. 1989). The claims presently recite that the polymer is optionally substituted with hydroxy, methyl, or methoxy groups. Support for this recitation can be found, *inter alia*, on page 6, lines 18-20, of the application as filed. There is no ambiguity as to which alternatives are covered. Applicants request that this rejection be withdrawn.

Claims 4 and 5 were rejected as allegedly indefinite in view of the recitation "derivatives thereof." New claims 13 and 14 correspond to original claims 4 and 5. The

Office asserted that the term "derivative" is not one which has a universally accepted meaning in the art. Claims 13 and 14 recite derivatives "reactive for linking the antibody fragment and polymer." Support for this recitation can be found, *inter alia*, on page 6, lines 26-28, of the application as filed. Applicants request that this rejection be withdrawn.

Claim 5 was rejected as allegedly indefinite because, per the Office, it is unclear if the phrase "polymer" is modifying both "methoxy(polyethylene glycol) and derivatives thereof", or just "derivatives thereof." Applicants have placed a comma after "methoxy(polyethylene glycol)" to indicate that the derivatives are of methoxy(polyethylene glycol). Applicants request that this rejection be withdrawn.

Claims 6 and 7 have been cancelled and there are no replacement claims. The rejection of these claims has been rendered moot.

Rejections Under 35 USC § 112, First Paragraph

Claims 1-7, 9 and 10 were rejected under 35 USC § 112, first paragraph, as allegedly not enabled for just any antibody fragments, only Fab and Fab'. Claim 11 corresponds to original claim 1. Claim 11 recites, *inter alia*, that the fragment consists of a V_H domain covalently linked to a C_H1 domain and a V_L domain covalently linked to a C_L domain. It is expected that this rejection has been obviated by amendment.

Rejections Under 35 USC § 102

Claims 1-4 and 6-10 were rejected under 35 USC 102(b) as allegedly anticipated by Pedley et al. Applicants traverse this rejection.

Claim 11 specifies that the polymer is covalently linked to one cysteine residue in the hinge region. This recitation is clearly not shown in Pedley et al. In Pedley et al, PEG moieties are attached to whole antibodies, $F(ab')_2$ fragments, or Fab' fragments. In whole antibodies and $F(ab')_2$ fragments, the hinge region is intact. The hinge region cysteine residues all participate in inter-heavy chain disulphide bonds. There is no disclosure in Pedley et al of any reduction of the whole antibodies or the $F(ab')_2$ fragments. Thus, in those cases, it is impossible for the PEG moieties to be attached to the hinge region cysteines.

It is no doubt the case that, in order to produce the Fab' fragments, the hinge region cysteines in the $F(ab')_2$ fragments are reduced (see Pedley et al, page 1126, right hand column, 1st sentence in "Preparation of Fab' A5B7"). However, the reduced $F(ab')_2$ is immediately treated with: "... an excess of N-ethylmaleimide ... to alkylate the liberated

hinge thiols." (emphasis added) (see Pedley et al, page 1126, right hand column, 2nd sentence in "Preparation of Fab'A5B7"). Thus, in the Fab' fragments, the hinge region cysteine residues are alkylated and, therefore, cannot react with any PEG moiety.

Further, Pedley et al shows that the PEG moieties are attached to lysine residues, not cysteine residues. As can be seen from the top of the left hand column of page 1127 of Pedley et al, the PEG moieties are introduced by first treating the whole antibody or the fragments with Traut's Reagent. Traut's reagent reacts with the ε-amino group of lysine residues and introduces a thiol group linked to the protein chain through the lysine residue. See, for example, Example 2 of U.S. Patent No. 4,863,713. Indeed, on page 1129, second column, Pedley et al report that "the attachment of PEG to the lysine side chains of the proteins . . ." Lysine residues are randomly distributed throughout the antibody chains. Thus, the PEG moieties, even on the Fab' fragment, are attached to the protein chain(s) at random points via lysine residues.

It can thus be seen that Pedley et al does not disclose or suggest attaching polymer moieties to one hinge region cysteine residue, as recited in claim 11. Applicants request that this rejection be withdrawn.

Claims 1, 9, and 10 were rejected under 35 USC § 102(e), as allegedly anticipated by Griffiths et al. The Office alleges that Griffiths et al teach site specific attachment of PEG to thiols in an antigen binding fragment (Fab or Fab') outside the variable region, with an effector attached, and compositions comprising the same. Applicants traverse this rejection.

Claim 11 recites that the hinge region contains only one cysteine residue, and that the polymer is covalently attached to this single cysteine residue in the hinge region. Griffiths et al does not disclose or suggest the covalent attachment of a polymer to a single cysteine residue in the hinge region.

Griffiths et al does describe the attachment of PEG moieties to antibody fragments. Griffiths et al also indicates that the PEGylated fragments are covalently attached to radioactive technetium (Tc) atoms, so that the radiolabelled PEGylated fragments can be used in *in vivo* imaging. Griffiths et al indicates on page 5, lines 14 to 19 that the PEG moieties may be linked to the fragments: "... site-specifically to ... thiol groups in the hinge region of the molecule." It is not indicated whether the thiol group is a cysteine thiol group or a thiol

group introduced in another way, for instance, by use of Traut's Reagent on a lysine residue. Certainly, there are no details as to how this should be achieved.

The further details on page 6, lines 20 to 38, of Griffiths et al, are not helpful, as these are, in fact, confusing. Griffiths et al indicates that there are two bivalent antibody fragments, $F(ab')_2$ and $F(ab)_2$. According to Griffiths et al, the former is made by pepsin cleavage of a whole antibody and the latter is made by papain cleavage. However, this is only partly correct. An $F(ab')_2$ fragment can be produced by pepsin cleavage, as pepsin cleaves on the C-terminal side of the hinge. Notably, in a $F(ab')_2$ fragment, the hinge region cysteines all participate in interchain disulphide bonds. Papain, however, cleaves on the N-terminal side of the hinge and therefore produces Fab fragments. Such Fab fragments do not include a hinge region. (The hinge region remains with the CH2 and CH3 domains to form the Fc fragment.) Thus, in neither case will it be possible to covalently link a hinge region disulphide bond to a PEG moiety.

It is also to be noted that Griffiths et al only contemplates the use of natural antibodies to produce its Tc-labelled antibodies or antibody fragments. There is no teaching or suggestion of modifying an antibody or antibody fragment prior to attaching the PEG moiety. It is very well known by those skilled in the art that, in all natural antibodies, the hinge region contains at least **two** inter-heavy chain disulphide bonds. In most cases there are many more than two disulphide bonds. Therefore, even if it were possible to make sense of Griffiths et al, it would not be possible to produce an antibody fragment having only one cysteine residue in the hinge region, following Griffiths et al.

It should also be noted that the authors of Griffiths et al did not disclose or suggest that PEG moieties would be linked to hinge region cysteines. The passage at column 4, line 47, through column 5, line 3, of Griffiths et al discusses the linking of the radioactive Tc atoms to the PEGylated antibody fragment. It can be seen from this passage that it is the intention of the authors that the Tc atoms should be attached to the hinge region thiols. If this is the case, then it follows that the PEG moieties cannot have been attached to the hinge region thiols. The examples confirm this. In Example 1, the PEG moieties are attached to lysine residues and then in Examples 2 to 4 the Tc atoms are attached to hinge thiols. In Example 7, the PEG moieties are attached to carbohydrate groups and, again, in Examples 8 and 9 the Tc atoms are attached to the hinge thiols.

It is therefore submitted that Griffiths et al does not disclose a modified monovalent antibody fragment as now claimed wherein a polymer is covalently linked to one cysteine in the hinge region. Thus, claim 11 is novel over Griffiths et al. Applicants request that this rejection be withdrawn.

Rejections Under 35 USC §103

Claims 1-10 were rejected as allegedly obvious over Pedley et al in view of Goodson et al, and in view of Woghiren et al. Applicants traverse this rejection.

For the reasons stated in the discussion of Pedley et al above, discussion incorporated herein, Pedley et al does not disclose or suggest the invention of claim 11. Specifically, Pedley et al does not disclose or suggest a polymer molecule to a cysteine residue, much less a single cysteine residue in the hinge region. Although the Office reports that the remaining references describe the modification of other proteins by attaching methoxy(polyethylene glycol) to a cysteine, the Office has not shown any motivation to modify Pedley et al to attach the polymer to a cysteine instead of lysines. Regardless, even if combined, the references do not disclose or suggest attaching the polymer to a single cysteine in the hinge region. Applicants request that this rejection be withdrawn.

Applicants note the prior art listed as pertinent but not relied upon, and reserve the right to respond to any rejections over the same if, and when, they are levied.

CONCLUSION

Applicants submit that all claims are in condition for allowance, and respectfully requests early notification of the same. If the Examiner disagrees, he is requested to contact the undersigned at the number provided below.

Respectfully submitted,

/Doreen Yatko Trujillo/

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Doreen Yatko Trujillo
Registration No. 35,719

COZEN O'CONNOR, P.C.
1900 Market Street, 7th Floor
Philadelphia, PA 19103-3508
(215) 665-5593 – Telephone
(215) 701-2005 - Facsimile